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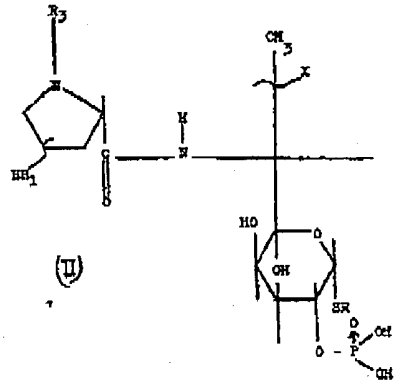
(54) PHARMACEUTICAL COMPOSITIONS COMPRISING LINCOMYCIN DERIVATIVES

(71) We, THE UPJOHN COMPANY, a corporation organized and existing under the laws of the State of Delaware, United States of America, of 301 Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is an improvement in or modification of that described and claimed in our copending application No. 53182/67 (Serial No. 1,211,380).

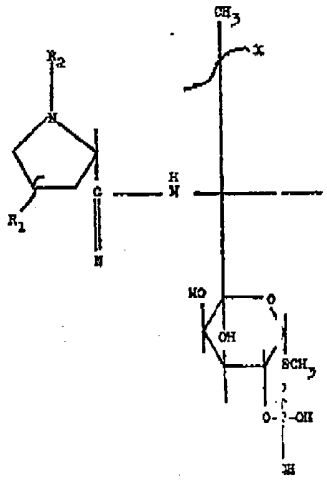
In copending application No. 53182/67 there are described and claimed antibacterial compounds of the general formula:—



(II)

and the salts thereof wherein X is OH, chlorine, or bromine, R and HR_1 are the same or different alkyl of not more than 20 carbon atoms, advantageously not more than 8 carbon atoms, cycloalkyl of from 3 to not more than 8 carbon atoms or aralkyl of not more than 12 carbon atoms, advantageously not more than 8 carbon atoms; and R_3 is hydrogen, alkyl of not more than 20 carbon atoms, advantageously not more than 8 carbon atoms, cycloalkyl of from 3 to not more than 8 carbon atoms or aralkyl of not more than 12 carbon atoms, advantageously not more than 8 carbon atoms and bactericidal compositions comprising as the active ingredient one of such compounds. Such bactericidal compositions in the form of an aqueous solution and a syrup are disclosed herein.

The present invention is directed to pharmaceutical and veterinary compositions comprising as the active ingredient a compound of the general formula:—



(I)

wherein X is hydroxy, chlorine, or bromine, R_1 is alkyl of C_{1-8}, cycloalkyl of C_{3-8}, or aralkyl of C_{7-12}, and R_2 is hydrogen, alkyl of C_{1-8}, cycloalkyl of C_{3-8}, or aralkyl of C_{7-12}, or a pharmaceutically acceptable salt thereof in the form of capsules, tablets, granules, parenteral solutions, topical ointments, creams,

opthalmic ointments, eye and ear drops, troches, rectal suppositories and mestitus ointments.

The invention also provides an oral syrup comprising as active ingredient one of the compounds of the general formula I and a sulpha drug.

Furthermore the invention provides an animal feed in solid form comprising a solid feed mix and a compound of the above general formula I.

Typical, but not all, therapeutic compounds of this invention include the following as referred to the above formula I:

R_1	R_2	X
trans n-propyl	methyl	—OH (R) isomer
" "	hydrogen	" " "
" "	ethyl	" " "
" "	isopropyl	" " "
" "	n-butyl	" " "
" "	cyclohexyl	" " "
n-pentyl	methyl	" " "
"	hydrogen	" " "
"	n-butyl	" " "
N-hexyl	methyl	" " "
"	hydrogen	" " "
"	n-butyl	" " "
trans n-propyl	methyl	—Cl (S) isomer
" "	hydrogen	" " "
" "	ethyl	" " "
" "	isopropyl	" " "
" "	n-butyl	" " "
" "	cyclohexyl	" " "
n-pentyl	methyl	" " "
"	hydrogen	" " "
"	n-butyl	" " "
trans-n-propyl	methyl	—Br (S) isomer
n-pentyl	hydrogen	" " "

In the above formula 1, the vertical wavy line $\int$ is used to indicate that the group R_1 can be in position *cis* (below the plane of the ring) or *trans* (above the plane of the ring), with respect to the carbonyl group. The horizontal wavy line $\sim$ is used to indicate that both epimers are to be included, i.e. the D-erythro configuration and L-*threo* configuration are intended.

Examples of alkyl are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, and octyl and isomeric forms thereof. Examples of cycloalkyl are cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 2-methylcyclopentyl, 2,3-dimethylcyclobutyl, 4-methylcyclobutyl, and 3-cyclopentylpropyl. Examples of aralkyl are benzyl, phenethyl, α-phenylpropyl, and α-naphthylmethyl.

The compounds of the formula 1 can be prepared by the methods disclosed in our copending application No. 53182/67 (Serial No. 1,211,380).

Further, the invention relates to a method for combating and/or preventing bacterial infections in animals, excluding humans, which comprises administering to said animals a compound of the formula 1 or a pharmaceutically acceptable salt thereof.

The compounds of the invention have essentially the same antibacterial spectrum *in vivo* as the antibiotic lincomycin and can be used for the same purposes as lincomycin. The compounds of the invention are particularly useful for oral administration to animals, including birds, because they lack the bitter taste of lincomycin.

The compositions of the present invention are presented for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, and oral solutions or suspension, and oil-water emulsions containing suitable quantities of a compound of formula 1 or its pharmacologically acceptable salts.

For oral administration either solid or fluid unit dosage forms can be prepared. For preparing solid compositions such as tablets, the principal active ingredient is mixed with conventional ingredients such as talc, magnesium stearate, dicalcium phosphate, magnesium aluminum silicate, calcium sulfate, starch, lactose, acacia, methyl cellulose, and functionally similar materials as pharmaceutical diluents or carriers. The tablets can be laminated or otherwise compounded to provide a dosage form affording the advantage of prolonged or delayed action or predetermined successive action of the enclosed medication. For example, the tablet can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former.

Alternatively, the two component system can be utilized for preparing tablets containing two or more incompatible active ingredients. Wafers are prepared in the same manner as tablets, differing only in shape and the inclusion of sucrose or other sweetener and flavor. In their simplest embodiment, capsules, like tablets, are prepared by mixing the antibiotic with an inert pharmaceutical diluent and filling the mixture into a hard gelatin capsule of appropriate size. In another embodiment, capsules are prepared by filling hard gelatin capsules with polymeric acid coated beads containing the antibiotic. Soft gelatin capsules are prepared by machine encapsulation of a slurry of the antibiotic with an acceptable vegetable oil, light liquid petrolatum or other inert oil.

Fluid unit dosage forms for oral administration such as syrups, elixirs, and suspensions can be prepared. The water-soluble forms can be dissolved in an aqueous vehicle together with sugar, aromatic flavoring agents and preservatives to form a syrup. An elixir is prepared by using a hydro-alcoholic (ethanol) vehicle with suitable sweeteners such as sugar

and saccharin, together with an aromatic flavoring agent.

Suspensions can be prepared of the insoluble forms with a syrup vehicle with the aid of a suspending agent such as acacia, tragacanth, methylcellulose and the like.

Topical ointments can be prepared by dispersing the antibiotic in a suitable ointment base such as petrolatum, lanolin, polyethylene glycols, mixtures thereof, and the like. Advantageously, the antibiotic is finely divided by means of a colloid mill utilizing light liquid petrolatum as a levigating agent prior to dispersing in the ointment base. Topical creams and lotions are prepared by dispersing the antibiotic in the oil phase prior to the emulsification of the oil phase in water.

For parenteral administration, fluid unit dosage forms are prepared utilizing the antibiotic and a sterile vehicle, water being preferred. The antibiotic, depending on the form and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the water-soluble antibiotic can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampule and sealing. Advantageously, adjuvants such as a local anesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection is supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the antibiotic is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The antibiotic can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agents included in the composition to facilitate uniform distribution of the antibiotic.

The term unit dosage form as used in the specification and claims refers to physically discrete units suitable as unitary dosages for human subjects and animals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical diluent, carrier or vehicle. The specification for the novel unit dosage forms of this invention are dictated by and directly dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active material for therapeutic use in humans and animals, as disclosed in detail in this specification, these being features of the present invention. Examples of suitable dosage forms in accord with this invention are tablets, capsules, pills, troches, suppositories, powder packets, granules, wafers, cachets, ampules, vials, segregated multiples of any of the foregoing, and other forms as herein described.

In addition to the administration of a compound of formula 1 as the principal active ingredient of compositions for the treatment of the conditions with other types of compounds to obtain advantageous combinations of properties. Such combinations include a compound of formula 1 with antibiotics such as spectinomycin, chloramphenicol, tetracyclines (e.g. tetracycline, oxytetracycline and chlortetracycline), penicillin, erythromycin, novobiocin, kanamycin, streptomycin, neomycin, polymyxin, bacitracin, nystatin, and endomycin broaden the bacterial spectrum of the composition; steroids having anti-inflammatory activity such as hydrocortisone, prednisolone, methylprednisolone and fluprednisolone; analgesics such as aspirin, sodium salicylate, (acetylsilicylic acid)-anhydride, acetaminophen and silicylamide; antihistamines, such as chlorpheniramine maleate, diphenhydramine, promethazine and pyrathiazine; sulfa drugs such as sulfadiazine, sulfamethazine, sulfamerazine, sulfacetamide, sulfamethyloxazole, sulfamethizole, and the like; antifungals, such as undecylenic acid, sodium propionate, salicyanilide, sodium caprylate, and hexetidine; and the vitamins.

The dosage of a compound of formula 1 for treatment depends on route of administration; the age, weight, and condition of the patient; and the particular disease to be treated. A dosage schedule of from about 50 to 500 mg., 1 to 4 times daily (every six hours), embraces the effective range for the treatment of most conditions for which the compositions are effective. For children the dosage is calculated on the basis of 6 to 8 mg./kg. by weight to be administered every six hours.

The antibiotic is compounded with a suitable pharmaceutical carrier in unit dosage form for convenient and effective administration. In the preferred embodiments of this invention, the dosage unit contains a compound of formula 1 in: 50, 100, 200 and 500 mg. amounts for systemic treatment; in 0.25, 0.5, 1, 2 and 5% amounts for topical or localised treatment; and 5 to 25% w/v for parenteral treatment. The dosage of compositions containing a compound of formula 1 and one or more other active ingredients is to be determined with reference to the usual dosage of each such ingredient.

The following examples are illustrative of the best mode contemplated by the inventors for carrying out their invention and are not to be construed as limiting:

EXAMPLE 1

Capsules

One thousand two-piece hard gelatin cap-

sules for oral use, each containing 200 mg. of lincomycin-2-phosphate are prepared from the following types and amounts of materials:

Lincomycin-2-phosphate	200 gm.
Corn starch	150 gm.
Talc	75 gm.
Magnesium stearate	2.5 gm.

The materials are thoroughly mixed and then encapsulated in the usual manner.

The foregoing capsules are useful for the systemic treatment of infection in adult humans by the oral administration of 1 capsule every 4 hours.

Using the procedure above, capsules are similarly prepared containing lincomycin-2-phosphate in 50, 100, and 500 mg. amounts by substituting 50, 100 and 500 gm. of lincomycin-2-phosphate for the 200 gm. used above.

Example 2
Capsules

One thousand two-piece hard gelatin capsules for oral use, each containing 200 mg. of lincomycin-2-phosphate and 250 mg. of tetracycline hydrochloride, are prepared from the following types and amounts of ingredients:

Lincomycin-2-phosphate	200 gm.
Tetracycline hydrochloride	250 gm.
Talc	75 gm.
Magnesium stearate	2.5 gm.

The ingredients are thoroughly mixed and then encapsulated in the usual manner.

The foregoing capsules are useful for the systemic treatment of infection in adult humans by the oral administration of 1 capsule every 6 hours.

Using the procedure above, capsules are similarly prepared containing lincomycin-2-phosphate and each of the following antibiotics in place of tetracycline by substituting 250 gm. of such other antibiotic for tetracycline: chloramphenicol, oxytetracycline, chlortetracycline, fumagillin, erythromycin, streptomycin, dihydrostreptomycin and novobiocin. When a penicilin, such as potassium penicillin G, is to be used in place of tetracycline, 250,000 units per capsule is employed.

Such combination products are useful for the systemic treatment of mixed infections in adult humans by the oral administration of 1 capsule every 6 hours.

Example 3
Tablets

One thousands tablets for oral use, each containing 500 mg. of lincomycin-2-phosphate are prepared from the following types and amounts of materials:—

Lincomycin-2-phosphate	500 gm.
Lactose	125 gm.
Corn starch	65 gm.
Magnesium stearate	7.5 gm.
Light liquid petrolatum	3 gm.

The ingredients are thoroughly mixed and slugged. The slugs are broken down by forcing through a number sixteen screen. The resulting granules are then compressed into tablets, each tablet containing 500 mg. of lincomycin-2-phosphate.

The foregoing tablets are useful for systemic treatment of infections in adult humans by oral administration of 1 tablet every 4 hours.

Using the above procedure, except for reducing the amount of lincomycin-2-phosphate to 200 gm., tablets containing 200 mg of lincomycin-2-phosphate are prepared.

Example 4
Tablets

One thousand oral tablets, each containing 200 mg. of lincomycin-2-phosphate and a total of 250 mg. (83.3 mg. each) of sulfadiazine, sulfamerazine, and sulfamethazine, are prepared from the following types and amounts of materials:

Lincomycin-2-phosphate	200 gm.
Sulfadiazine	83.3 gm.
Sulfamerazine	83.3 gm.
Sulfamethazine	83.3 gm.
Lactose	50 gm.
Corn starch	50 gm.
Calcium stearate	5.5 gm.
Light liquid petrolatum	5 gm.

The ingredients are thoroughly mixed and slugged. The slugs are broken down by forcing through a number sixteen screen. The resulting granules are then compressed into tablets, each containing 200 mg. of lincomycin-2-phosphate and a total of 250 mg. (83.3 mg. each) of sulfadiazine, sulfamerazine and sulfamethazine.

The foregoing tablets are useful for systemic treatment of infections by the oral administration of 4 tablets first and then 1 every six hours.

For the treatment of urinary infections, the triple sulfas in the above formulation is advantageously replaced by 250 gm. of sulfamethyldiazole or 250 gm. of sulfacetamide.

Example 5
Granules

2367 gm. of a granulation suitable for reconstitution with water prior to use is prepared from the following types and amounts of ingredients:

Lincomycin-2-phosphate	150 gm.
Tetracycline hydrochloride	150 gm.
Lecithin	5 gm.
Sucrose, powdered	2000 gm.
Flavor	60 gm.
Sodium metabisulfite	2 gm.

The tetracycline is finely divided and coated with the lecithin. The coated tetracycline, lincomycin-2-phosphate, sugar, flavor, and sodium metabisulfite are mixed together until thoroughly blended. The powder mixture is wetted with water and forced through a screen to form granules. The granules are dried and 23.67 gm. filled into 60 cc. bottles. Prior to use sufficient water is added to the granules to make 60 cc. of composition.

The foregoing composition is useful for systemic treatment of infection, particularly in children at a dose of one teaspoonful 4 times daily.

EXAMPLE 6

Oral syrup

One thousand cc. of an aqueous suspension for oral use, containing in each 5 cc. dose, one-half gram of total sulfas and 200 mg. of lincomycin-2-phosphate is prepared from the following types and amounts of ingredients:

Lincomycin-2-phosphate	40 gm.
Sulfadiazine	33.3 gm.
Sulfamethazine	33.3 gm.
Citric acid	2 gm.
Benzoic acid	1 gm.
Sucrose	700 gm.
Tragacanth	5 gm.
Lemon oil	2 cc.
Deionized water q.s.	1000 cc.

The citric acid, benzoic acid, sucrose, tragacanth, and lemon oil are dispersed in sufficient water to make 850 cc. of solution. The lincomycin-2-phosphate and finely powdered sulfas are stirred into syrup until uniformly distributed. Sufficient water is added to make 1000 cc.

The composition so prepared is useful in the systemic treatment of pneumonia in adult humans at a dose of 1 teaspoonful 4 times a day.

EXAMPLE 7

Parenteral solution

A sterile aqueous solution of intramuscular use, containing in 1 cc. 75 mg. of lincomycin-2-phosphate is prepared from the following types and amounts of materials:

Lincomycin-2-phosphate	75 gm.
Lidocaine hydrochloride	4 gm.
Methylparaben	2.5 gm.
Propylparaben	0.17 gm.
Water for injection q.s.	1000 cc.

The ingredients are dissolved in the water and the solution sterilized by filtration. The sterile solution is filled into vials and the vials sealed.

EXAMPLE 8

Parenteral solution

A sterile aqueous solution for intramuscular use, containing in 1 cc. 250 mg. of lincomycin-2-phosphate, as the Na salt is prepared from the following types and amounts of ingredients:

Lincomycin-2-phosphate	250 gm.
Sodium hydroxide 10% solution q.s.	
Water for injection q.s.	1000 cc.

The lincomyincin-2-phosphate is added to the water and sufficient sodium hydroxide added to form a solution and the solution sterilized by filtration. The sterile solution, in the amount of 2 cc., is aseptically filled into sterile vials and frozen. The water is removed under high vacuum and the vials containing the lyophilized powder are sealed. Just prior to use, sufficient sterile water for injection to make 2 cc. of solution is added to the vial.

EXAMPLE 9

Topical ointment

One thousand gm. of 0.2% ointment is prepared from the following types and amounts of ingredients:

Lincomycin-2-phosphate	2.5 gm.
Zinc oxide	50 gm.
Calamine	50 gm.
Liquid petrolatum (heavy)	250 gm.
Wool fat	200 gm.
White petrolatum q.s.	1000 gm.

The white petrolatum and wool fat are melted and 100 gm. of liquid petrolatum added thereto. The lincomycin-2-phosphate, zinc oxide and calamine are added to the remaining liquid petrolatum and the mixture milled until the powders are finely divided and uniformly dispersed. The powder mixture is stirred into the white petrolatum mixture and stirring continued until the ointment congeals.

The foregoing ointment is usefully applied topically to the skin of mammals for the treatment of infection.

The foregoing composition can be prepared by omitting the zinc oxide and calamine.

Following the procedure above, ointments are similarly prepared containing lincomycin-2-phosphate in 0.5, 1, 2 and 5% amounts by substituting 5, 10, 20, and 50 gm. of lincomycin-2-phosphate for the 2.5 gm. used above.

EXAMPLE 10

Cream

One thousand gm. of a vaginal cream are

sules for oral use, each containing 200 mg. of lincomycin-2-phosphate are prepared from the following types and amounts of materials:

Lincomycin-2-phosphate	200 gm.
Corn starch	150 gm.
Talc	75 gm.
Magnesium stearate	2.5 gm.

The materials are thoroughly mixed and then encapsulated in the usual manner.

The foregoing capsules are useful for the systemic treatment of infection in adult humans by the oral adminstration of 1 capsule every 4 hours.

Using the procedure above, capsules are similarly prepared containing lincomycin-2-phosphate in 50, 100, and 500 mg. amounts by substituting 50, 100 and 500 gm. of lincomycin-2-phosphate for the 200 gm. used above.

Example 2
Capsules

One thousand two-piece hard gelatin capsules for oral use, each containing 200 mg. of lincomycin-2-phosphate and 250 mg. of tetracycline hydrochloride, are prepared from the following types and amounts of ingredients:

Lincomycin-2-phosphate	200 gm.
Tetracycline hydrochloride	250 gm.
Talc	75 gm.
Magnesium stearate	2.5 gm.

The ingredients are thoroughly mixed and then encapsulated in the usual manner.

The foregoing capsules are useful for the systemic treatment of infection in adult humans by the oral administration of 1 capsule every 6 hours.

Using the procedure above, capsules are similarly prepared containing lincomycin-2-phosphate and each of the following antibiotics in place of tetracycline by substituting 250 gm. of such other antibiotic for tetracycline: chloramphenicol, oxytetracycline, chlortetracycline, furnagillin, ethythromycin, streptomycin, dihydrostreptomycin and novobiocin. When a penicillin, such as potassium penicillin G, is to be used in place of tetracycline, 250,000 units per capsule is employed.

Such combination products are useful for the systemic treatment of mixed infections in adult humans by the oral administration of 1 capsule every 6 hours.

Example 3
Tablets

One thousands tablets for oral use, each containing 500 mg. of lincomycin-2-phosphate are prepared from the following types and amounts of materials:—

Lincomycin-2-phosphate	500 gm.
Lactose	125 gm.
Corn starch	65 gm.
Magnesium stearate	7.5 gm.
Light liquid petrolatum	3 gm.

The ingredients are thoroughly mixed and slugged. The slugs are broken down by forcing through a number sixteen screen. The resulting granules are then compressed into tablets, each tablet containing 500 mg. of lincomycin-2-phosphate.

The foregoing tablets are useful for systemic treatment of infections in adult humans by oral administration of 1 tablet every 4 hours.

Using the above procedure, except for reducing the amount of lincomycin-2-phosphate to 200 gm., tablets containing 200 mg of lincomycin-2-phosphate are prepared.

Example 4
Tablets

One thousand oral tablets, each containing 200 mg. of lincomycin-2-phosphate and a total of 250 mg. (83.3 mg. each) of sulfadiazine, sulfamerazine, and sulfamethazine, are prepared from the following types and amounts of materials:

Lincomycin-2-phosphate	200 gm.
Sulfadiazine	83.3 gm.
Sulfamerazine	83.3 gm.
Sulfamethazine	83.3 gm.
Lactose	50 gm.
Corn starch	50 gm.
Calcium stearate	5.5 gm.
Light liquid petrolatum	5 gm.

The ingredients are thoroughly mixed and slugged. The slugs are broken down by forcing through a number sixteen screen. The resulting granules are then compressed into tablets, each containing 200 mg. of lincomycin-2-phosphate and a total of 250 mg. (83.3 mg. each) of sulfadiazine, sulfamerazine and sulfamethazine.

The foregoing tablets are useful for systemic treatment of infections by the oral administration of 4 tablets first and then 1 every six hours.

For the treatment of urinary infections, the triple sulfas in the above formulation is advantageously replaced by 250 gm. of sulfamethyldiazole or 250 gm. of sulfacetamide.

Example 5
Granules

2367 gm. of a granulation suitable for reconstitution with water prior to use is prepared from the following types and amounts of ingredients:

prepared from the following types and amounts of ingredients:

Lincomycin-2-phosphate	50 gm.
Tegacid Regular*	150 gm.
Spermaceti	100 gm.
Propylene glycol	50 gm.
Polysorbate 80	5 gm.
Methylparaben	1 gm.
Deionized water q.s.	1000 gm.

*Self-emulsifying glyceryl monostearate from Gold-schmidt Chemical Corporation, New York, N.Y.

The Tegacid and spermaceti are melted together at a temperature of 70—80° C. The methylparaben is dissolved in about 500 gm. of water and the propylene glycol, polysorbate 80, and lincomycin-2-phosphate are added in turn, maintaining a temperature of 75—80° C. The methylparaben mixture is added slowly to the Tegacid and spermaceti melt, with constant stirring. The addition is continued for at least 30 minutes with continued stirring until the temperature has dropped to 40—45° C. The pH of the final cream is adjusted to 3.5 by incorporation 2.5 gm. of citric acid and 0.2 gm. of dibasic sodium phosphate dissolved in about 50 gm. of water. Finally, sufficient water is added to bring the final weight to 1000 gm. and the preparation stirred to maintain homogeneity until cooled and congealed.

The foregoing composition is useful for the treatment of vaginal infections in humans.

EXAMPLE 11

Ointment, ophthalmic

One thousand gm. of an ophthalmic ointment containing 0.5% lincomycin-2-phosphate are prepared from the following types and amounts of ingredients:

Lincomycin-2-phosphate	5 gm.
Bacitracin	12.2 gm.
Polymyxin B sulfate (10,000 units/mg.)	1 gm.
Light liquid petrolatum	250 gm.
Wool fat	200 gm.
White petrolatum q.s.	1000 gm.

The antibiotics are finely divided by means of an air micronizer and added to the light liquid petrolatum. The mixture is passed through a colloid mill to uniformly distribute the antibiotics. The wool fat and white petrolatum are melted together, strained, and the temperature adjusted to 45—50° C. The liquid petrolatum slurry is added and the ointment stirred until congealed. Suitably, the ointment is packaged in one dram ophthalmic tubes.

The foregoing ointment is usefully applied to the eye for treatment of localized infection in humans and other animals.

Advantageously, the foregoing composition can contain 5 gm. (0.5%) of methylprednisolone for the treatment of inflammation, and, alternatively, the bacitracin and polymyxin B sulfate can be omitted.

EXAMPLE 12

Eye-ear drops

One thousand cc. of a sterile aqueous solution for eye or ear use containing 10 mg. of lincomycin-2-phosphate and 10 mg. of prednisolone succinate sodium in each cc. is prepared from the following types and amounts of ingredients:

Lincomycin-2-phosphate	10 gm.
Prednisolone-succinate sodium	10 gm.
Sodium citrate	4.5 gm.
Polyethylene glycol 4000	120 gm.
Myristyl-γ-picolinium chloride	0.2 gm.
Polyvinylpyrrolidone	1 gm.
Deionized water q.s. ad	1000 cc.

The ingredients are dissolved in the water and the resulting solution is sterilized by filtration. The solution is aseptically filled into sterile dropper containers.

The composition so prepared is useful in the topical treatment of inflammation and infection of the eye and ear as well as other sensitive tissues of the animal body.

EXAMPLE 13

Troches

Tenthousand troches are prepared from the following types and amounts of ingredients:

Lincomycin-2-phosphate	100gm.
Neomycin sulfate	50 gm.
Polymyxin B sulfate (10,000 units/mg.)	1 gm.
Ethyl aminobenzoate	50 gm.
Calcium stearate	150 gm.
Powered sucrose q.s.	5000 gm.

The powdered materials are mixed thoroughly and then compressed into half gram troches following the usual techniques for the preparation of compressed tablets.

The troches are held in the mouth and allowed to dissolve slowly to provide treatment for the mouth and throat of

EXAMPLE 14

Suppository, rectal

One thousand suppositories, each weighing 2.5 gms. and containing 100 mg. of lincomycin-2-phosphate are prepared from the following types and amounts of ingredients.

Lincomycin-2-phosphate	100 gm.
Polymyxin B sulfate (10,000 units/mg.)	1.25 gm.
6α-methylprednisolone	1 gm.
Ethyl aminobenzoate	75 gm.
Zinc oxide	62.5 gm.
Propylene glycol	162.5 gm.
Polyethylene glycol 4000 q.s.	2500 gm.

The lincomycin-2-phosphate, polymyxin B sulfate, 6-methylprednisolone, ethyl aminobenzoate, and zinc oxide are added to the propylene glycol and the mixture milled until the powders are finely divided and uniformly dispersed. The polyethylene glycol 4000 is melted and the propylene glycol dispersion added slowly with stirring. The suspension is poured into unchilled molds at 40° C. The composition is allowed to cool and solidify and then removed from the mold and each suppository foil wrapped.

The foregoing suppositories are inserted rectally for local treatment of inflammation and infection.

Alternatively, the foregoing composition can be prepared omitting the steroid.

EXAMPLE 15

Mastitis ointment

One thousand gm. of an ointment for the treatment of mastitis in dairy cattle is prepared from the following types and amounts of ingredients:

Lincomycin-2-phosphate	50 gm.
Prednisolone acetate	0.5 gm.
Light liquid petrolatum	300 gm.
Chlorobutanol, anhydrous	5 gm.
Polysorbate 80	5 gm.
2% Aluminum monostearate-peanut oil gel	400 gm.
White petrolatum q.s.	1000 gm.

The lincomycin-2-phosphate and prednisolone acetate are milled with the light liquid petrolatum until finely divided and uniformly dispersed. The chlorobutanol, polysorbate 80, peanut oil gel and white petrolatum are heated to 120° F. to form a melt and the liquid petrolatum dispersion stirred in. With continued stirring the dispersion is allowed to cool (and congeal) to room temperature and is filled into disposable mastitis syringes in 10 gm. doses.

EXAMPLE 16

Animal feed

One thousand gm. of a feed mix is prepared from the following types and amounts of ingredients:—

Lincomycin-2-phosphate	10 gm.
Soybean meal	400 gm.
Fish meal	400 gm.
Wheat germ oil	50 gm.
Sorghum molasses	140 gm.

The ingredients are mixed together and pressed into pellets.

The composition can be fed to laboratory animals, i.e., rats, mice, guinea pigs, and rabbits for prophylaxis during shipping.

For larger animals, the composition can be added to the animal's regular feed in an amount calculated to give the desired dose of lincomycin-2-phosphate.

EXAMPLE 17

Following the procedure of each of the preceding Examples 1 and 3, each member selected from sodium novobiocin, calcium novobiocin, chlortetracycline hydrochloride, oxytetracycline hydrochloride, tetracycline, tetracycline hydrochloride, and tetracycline phosphate complex is added in 50, 100, and 250 gm. amounts to provide a combination having a wider spectrum of therapeutic effectiveness in the treatment of infectious diseases resulting from mixed organisms susceptible to lincomycin-2-phosphate as indicated in the present specification and the above indicated antibiotics as already well known to the medical art.

EXAMPLE 18

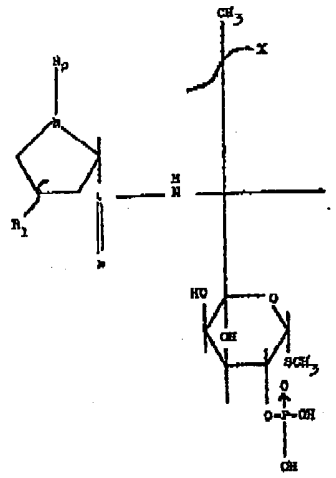
Following the procedure of the preceding Examples 1 through 16, inclusive, each member selected from lincomycin-2-phosphate, hemiammonium salt, 7(S) - chloro - 7 - deoxy-lincomycin - 2 - phosphate, 7(S) - chloro - 7 - deoxy - 1′ - demethyllincomycin - 2 - phosphate, 7(S) - chloro - 7 - deoxy - 4′ - depropyl - 4′ - pentyl - 1′ - demethyllincomycin - 2 - phosphate, 7(S) - chloro - 7 - deoxy - 4′ - depropyl - 4′ - pentyl - 1′ - demethyl - lincomycin - 2 - phosphate, calcium salt, or 7(S) - chloro - 7 - deoxy - 4′ - depropyl - 4′ - pentyl - 1′ - demethyllincomycin - 2 - phosphate, magnesium salt is substituted in an equivalent amount for the lincomycin-2-phosphate shown in the example and provides similar therapeutic properties.

EXAMPLE 19

Following the procedure of the preceding Example 1 through 5, 9 through 11, and 13 through 16, inclusive, each member selected from 7(S) - chloro - 7 - deoxylincomycin - 2 - phosphate, calcium salt, 7(S) - chloro - 7 - deoxylincomycin - 2 - phosphate, magnesium salt, 7(S) - chloro - 7 - deoxy - 1′ - demethyl-lincomycin - 2 - phosphate, calcium salt or 7(S) - chloro - 7 - deoxy - 1′ demethyllincomycin - 2 - phosphate, magnesium salt is substituted in an equivalent amount for the lincomycin - 2 - phosphate shown in the example and provides similar therapeutic properties.

WHAT WE CLAIM IS:—

1. A pharmaceutical or veterinary composition comprising as the active ingredient a compound having the general formula:—



wherein X is hydroxy, chlorine or bromine, R_1 is alkyl of C_{2-15}, cycloalkyl of C_{3-15} or aralkyl of C_{7-19} and R_2 is hydrogen, alkyl of C_{1-5}, cycloalkyl of C_{3-5} or aralkyl of C_7 to C_{12} or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable solid carrier.

2. A composition according to claim 1 in the form of a capsule.

3. A composition according to claim 1 in the form of a tablet.

4. A composition according to claim 1 in the form of granules.

5. A pharmaceutical or veterinary composition for parenteral adminstration comprising as the active ingredient a compound as defined in claim 1 together with a sterile aqueous vehicle.

6. A pharmaceutical or veterinary composition comprising as the active ingredient a compound as defined in claim 1 in the form of a soft gelatin capsule.

7. A composition as claimed in claim 6 wherein the active ingredient is in the form of a slurry with an acceptable vegetable oil, light liquid petrolatum or other inert oil.

8. A pharmaceutical or veterinary composition comprising as active ingredient a compound as defined in claim 1 dispersed in an ointment base.

9. A composition as claimed in claim 8 wherein the ointment base is petrolatum, lanolin, a polyethylene glycol or mixtures thereof.

10. A pharmaceutical or veterinary composition comprising as the active ingredient a compound as defined in claim 1 in the form of a topical cream or lotion.

11. A composition as claimed in claim 10 and comprising an emulsification in water of a dispersion of the active ingredient in oil phase.

12. A composition as claimed in any preceding claim and comprising also an antibiotic, a steroid, an analgesic an antihistamine, one or more sulpha drugs or an antifungal agent.

13. A pharmaceutical or veterinary composition in the form of a syrup and comprising as the active ingredient a compound as defined in claim 1 and one or more sulpha drugs.

14. An animal feed comprising a solid feed mix and a compound as defined in claim 1.

15. A pharmaceutical or veterinary composition comprising as the active ingredient a compound as defined in claim 1 substantially as herein described with reference to the Examples.

16. A method for combating and/or preventing bacterial infections in animals, excluding humans, which comprises administering to said animals a compound as defined in claim 1 or a pharmaceutically acceptable salt thereof.

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